General

Guideline Title

Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines for *IFNL3 (IL28B) genotype* and PEG interferon-α–based regimens.

Bibliographic Source(s)

Muir AJ, Gong L, Johnson SG, Lee MT, Williams MS, Klein TE, Caudle KE, Nelson DR, Clinical Pharmacogenetics Implementation Consortium (CPIC). Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines for IFNL3 (IL28B) genotype and PEG interferon-alpha-based regimens. Clin Pharmacol Ther. 2014 Feb;95(2):141-6. [40 references] PubMed

Guideline Status

This is the current release of the guideline.

Recommendations

Major Recommendations

The strength of therapeutic recommendations (Strong, Moderate, Optional) is defined at the end of the "Major Recommendations" field.

Gene: *IFNL3*

Genetic Test Interpretation

Laboratory results for *IFNL3* genotype are typically reported as reference single-nucleotide polymorphism identification number (rs) followed by the specific genotype (i.e., rs12979860 CC, CT, or TT) with accompanying interpretation (i.e., favorable genotype vs. unfavorable genotype). The assignment of the likely *IFNL3* phenotype, based on diplotypes, is summarized in Table 1 below.

Table 1. Assignment of Probable *IFNL3* Phenotypes Based on Genotypes

Observed Phenotype	Description	Genotype Definitions	Genotype rs12979860
Favorable response genotype	Increased likelihood of response (higher SVR rate) to PEG-IFN-α and RBV therapy as compared with patients with unfavorable response genotype	An individual carrying two favorable response alleles	CC
Unfavorable response	Decreased likelihood of response (lower SVR rate) to PEG-IFN-α and RBV therapy as compared with patients with favorable response	An individual carrying at least one unfavorable response	CT or TT

genotype Observed Phenotype	genotype Description	allele Genotype Definitions	Genotype rs12979860

PEG-IFN-α, pegylated interferon-α 2a or 2b; RBV, ribavirin; SVR, sustained virologic response.

Therapeutic Recommendations

Table 2 below summarizes the therapeutic recommendations for pegylated interferon α (PEG-IFN-α) and ribavirin (RBV) therapy based on *IFNL3* genotype. Treatment of hepatitis C virus (HCV) genotype 1 infection varies throughout the world currently because some regions have access to the new direct-acting antivirals in combination with PEG-IFN-α and RBV, whereas other regions have access only to PEG-IFN-α and RBV. The role of *IFNL3* genotyping depends on treatment selection. *IFNL3* genotype is only one factor that can influence response rates to PEG-IFN-α and RBV therapy in HCV genotype 1 infection and should be interpreted in the context of other clinical and genetic factors.

PEG-IFN-α and RBV

For patients treated with PEG-IFN-α and RBV alone, *IFNL3* genotype is the strongest pretreatment predictor of HCV treatment response. In the intention-to-treat analysis of the original discovery cohort with rs12979860, Caucasian patients with CC genotype were more likely than those with CT or TT genotype to have undetectable serum viral RNA by week 4 (28 vs. 5 and 5%, respectively; P <0.0001) and to achieve SVR (69% vs. 33% and 27%, respectively; P <0.0001). Similar patterns were observed in Hispanic and African- American patients in this cohort. HCV treatment is associated with significant side effects, and the likelihood of response treatment influences shared decision making between clinicians and patients about initiating treatment.

Protease Inhibitor Combination Regimens—Treatment Naive

For treatment-naive patients with genotype 1 infection who are treated with protease inhibitor combinations, all *IFNL3* genotypes have improved response rates as compared with patients treated with PEG-IFN-α and RBV only. However, patients with the favorable *IFNL3* genotype still have higher response rates with the protease inhibitor combination in treatment-naive patients, and these response rates may guide patients and clinicians in their treatment decisions. In the boceprevir phase III treatment naive study of combination with PEG-IFN-α and RBV, SVR rates for rs12979860 CC patients receiving boceprevir ranged from 80 to 82% as compared with 65% to 71% for CT patients and 59–65% for TT patients. Moreover, multivariate regression analysis revealed that rs12979860 CC genotype was a predictor of SVR as compared with CT (odds ratio = 2.6, 95% confidence interval = 1.3–5.1) and TT genotypes (odds ratio = 2.1, 95% confidence interval = 1.2–3.7).

Role of the Lead-in

Although *IFNL3* genotype is the strongest pretreatment predictor of response to IFN-α-based therapy, the use of the early on-treatment antiviral response has also been extensively evaluated. The *IFNL3* genotype is a marker for IFN responsiveness, and patients with the favorable *IFNL3* genotype are more likely to have significant reductions in HCV RNA during the first 4 weeks of therapy. The boceprevir combination regimen starts with 4 weeks of PEG-IFN-α and RBV, and boceprevir is added in the fifth week. In the analysis of the boceprevir phase III studies, SVR models that considered only baseline characteristics found that the *IFNL3* genotype was a predictor of SVR. When the lead-in response was added to these models, the *IFNL3* genotype was no longer a predictor. It has been proposed that these early kinetics minimize the value of the *IFNL3* genotype, but the lead-in response is known only for patients who have initiated therapy. For the patient who is considering whether or not to undergo HCV therapy with the boceprevir regimen, *IFNL3* genotype remains the most helpful predictor of likelihood of response.

Duration of Therapy

Duration of treatment is another important factor for clinicians and patients to consider before initiating PEG-IFN-α and RBV therapy because patients with favorable *IFNL3* genotypes are more likely to respond to shorter treatment courses. Patients receiving boceprevir are eligible for 24- to 28-week regimens instead of the standard 48-week regimen if HCV RNA is undetectable by week 8. In the boceprevir phase III clinical trial for treatment-naive patients, rs12979860 CC patients were more likely to have undetectable HCV RNA at week 8 (89%) than CT (53%) or TT (42%) patients. SVR rates ranged from 81% to 100% for all patients in whom HCV RNA was undetectable by week 8, regardless of *IFNL3* genotype. With telaprevir therapy, patients with undetectable HCV RNA by week 4 are eligible for a treatment regimen of only 24 weeks. Given the side-effect burden of PEG-IFN-α and RBV, the possibility of shorter treatment course may influence treatment choice for some patients.

Past Treatment

In general, patients who have failed previous IFN-α-based therapies are enriched for the unfavorable *IFNL3* genotype; therefore, *IFNL3* genotype is less likely to influence clinical decisions. Analysis of phase III boceprevir trial results for patients who were treatment experienced found that *IFNL3* genotype did not predict SVR. In patients with unclear records of their previous treatment or with questions about the quality of care received in a previous course of therapy, the *IFNL3* genotype can be considered a marker of IFN responsiveness that contributes to HCV treatment response.

IFNL3 Single-Nucleotide Polymorphism Concordance

Given that both rs12979860 and rs8099917 tests are available, clinicians may receive both pieces of data. The boceprevir phase III program conducted an analysis and found that combining rs12979860 and rs8099917 test results did not improve the strength of the association between the *IFNL3* genotype and SVR as compared with the results using rs12979860 genotype alone. This analysis also found instances of discordance between rs12979860 and rs8099917. Most rs12979860 CC patients had the favorable TT pattern at the rs8099917 locus. However, of the 426 patients with the favorable TT genotype at the rs8099917 locus, only 208 (48.8%) also had the favorable CC genotype at the rs12979860 locus. This analysis of the boceprevir program reported that both rs12979860 and rs8099917 predict SVR, but rs12979860 is more reliable in this group of patients.

Table 2. Recommendations for Use of PEG-IFN-α–Containing Regimens Based on *IFNL3* Genotype

Phenotype	Implications for PEG-IFN-α and RBV Therapy[a]	Implications for Protease Inhibitor Combinations with PEG-IFN-α and RBV Therapy	Classification of Recommendation[b]
Favorable response genotype	Approximately 70% chance for SVR[c] after 48 weeks of treatment. Consider implications before initiating PEG-IFN-α- and RBV-containing regimens.	Approximately 90% chance for SVR[c] after 24–48 weeks of treatment. Approximately 80–90% of patients are eligible for shortened therapy (24–28 weeks vs. 48 weeks).[d] Weighs in favor of using PEG-IFN-α- and RBV-containing regimens.	Strong
Unfavorable response genotype	Approximately 30% chance of SVR[c] after 48 weeks of treatment. Consider implications before initiating PEG-IFN-α- and RBV-containing regimens.	Approximately 60% chance of SVR[c] after 24–48 weeks of treatment. Approximately 50% of patients are eligible for shortened therapy regimens (24–28 weeks).[d] Consider implications before initiating PEG-IFN-α- and RBV-containing regimens.	Strong

HCV, hepatitis C virus; PEG-IFN-α, pegylated interferon-α 2a or 2b; RBV, ribavirin.

[a]In cases in which a protease inhibitor is not available.

[b]See Supplementary Tables S1–S4 online (see the "Availability of Companion Documents" field) for additional details regarding the three-tiered system used to grade the quality of evidence and strength of recommendations by the Clinical Pharmacogenetics Implementation Consortium.

[c]SVR, sustained virologic response (defined by undetectable serum viral RNA 12–24 weeks after the end of treatment). [d]Patients receiving boceprevir are eligible for treatment regimens of 24–28 weeks instead of the standard 48 weeks if HCV RNA is undetectable by week 8. Patients receiving telaprevir are eligible for 24 weeks of therapy instead of the standard 48 weeks if HCV RNA is undetectable by week 4.

Definitions:

Strength of Therapeutic Recommendations

Strong: The evidence is high quality and the desirable effects clearly outweigh the undesirable effects.

Moderate: There is a close or uncertain balance as to whether the evidence is high quality and the desirable clearly outweigh the undesirable effects.

Optional: The desirable effects are closely balanced with undesirable effects and there is room for differences of opinion as to the need for the recommended course of action.

Clinical Algorithm(s)

None provided

Scope

Disease/Condition(s)

Hepatitis C virus (HCV)

Guideline Category

Prevention

Risk Assessment

Treatment

Clinical Specialty

Gastroenterology

Infectious Diseases

Medical Genetics

Pharmacology

Intended Users

Advanced Practice Nurses

Pharmacists

Physician Assistants

Physicians

Guideline Objective(s)

To provide information regarding the clinical use of *IFNL3* (*IL28B*) genotyping to guide the use of pegylated interferon-α (PEG-IFN-α or PEG-IFN-α 2a and 2b) and ribavirin (RBV) combination therapy, including treatment with direct-acting antivirals approved for hepatitis C virus (HCV) genotype 1 infection

Target Population

Patients with hepatitis C virus (HCV) infection

Interventions and Practices Considered

Pegylated interferon-α (PEG-IFN-α)-based regimens based on *IFNL3* (*IL28B*) genotype:

- PEG-IFN-α
- PEG-IFN 2a and 2b
- Ribavirin (RBV)

Major Outcomes Considered

- Efficacy of antiviral treatment
- Side-effects of treatment

- Morbidity
- Mortality

Methodology

Methods Used to Collect/Select the Evidence

Searches of Electronic Databases

Description of Methods Used to Collect/Select the Evidence

Focused Literature Review

A literature search of the PubMed (1966 to January 2013) and Ovid MEDLINE (1950 to January 2013) database using the keywords ([IL28B OR interleukin 28] AND [peginterferon OR pegylated-interferon alpha OR PEG/IFN] AND genotype) was performed. Only articles available in English were reviewed.

Number of Source Documents

Not stated

Methods Used to Assess the Quality and Strength of the Evidence

Weighting According to a Rating Scheme (Scheme Given)

Rating Scheme for the Strength of the Evidence

Levels of Evidence Linking Genotype to Phenotype

High: Evidence includes consistent results from well-designed, well-conducted studies.

Moderate: Evidence is sufficient to determine effects, but the strength of the evidence is limited by the number, quality, or consistency of the individual studies; generalizability to routine practice; or indirect nature of the evidence.

Weak: Evidence is insufficient to assess the effects on health outcomes because of limited number or power of studies, important flaws in their design or conduct, gaps in the chain of evidence, or lack of information.

Methods Used to Analyze the Evidence

Systematic Review with Evidence Tables

Description of the Methods Used to Analyze the Evidence

The evidence summarized in Supplemental Table S4 (see the "Availability of Companion Documents" field) has been graded using the three tiered system required by the Clinical Pharmacogenetics Implementation Consortium.

Methods Used to Formulate the Recommendations

Expert Consensus

Description of Methods Used to Formulate the Recommendations

Overall, the therapeutic recommendations are simplified to allow rapid interpretation by clinicians. The authors chose to use a slight modification of a transparent and simple system for just three categories for recommendations adopted from the rating scale for evidence-based recommendations on the use of retroviral agents found at http://aidsinfo.nih.gov/contentfiles/AdultandAdolescentGL.pdf (see the "Rating Scheme for the Strength of the Recommendations" field).

Rating Scheme for the Strength of the Recommendations

Strength of Therapeutic Recommendations

Strong: The evidence is high quality and the desirable effects clearly outweigh the undesirable effects.

Moderate: There is a close or uncertain balance as to whether the evidence is high quality and the desirable clearly outweigh the undesirable effects.

Optional: The desirable effects are closely balanced with undesirable effects and there is room for differences of opinion as to the need for the recommended course of action.

Cost Analysis

A formal cost analysis was not performed and published cost analyses were not reviewed.

Method of Guideline Validation

Peer Review

Description of Method of Guideline Validation

Not stated

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The type of supporting evidence is identified and graded for each recommendation (see the "Major Recommendations" field).

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

IFNL3 genotype testing is the strongest baseline predictor of response to pegylated interferon-α (PEG-IFN-α) and ribavirin (RBV) therapy in previously untreated patients and can be used by patients and clinicians as part of the shared decision-making process for initiating treatment for hepatitis C virus (HCV) infection.

Potential Harms

- Patients considering hepatitis C virus (HCV) therapy are confronted with medications with significant side effects and varying response rates. The side-effect profile of HCV regimens should be considered independently from the likelihood of response according to *IFNL3*

genotype.
- Although not studied formally, knowledge of a reduced likelihood of response may result in fewer patients receiving HCV therapy that might have been effective.

Qualifying Statements

Qualifying Statements

Qualifying Statements

Caveats: Appropriate Use and/or Potential Misuse of Genetic Tests

IFNL3 genotype is a strong predictor of treatment response for patients receiving treatment for chronic hepatitis C virus (HCV) infection. However, genotyping alone does not provide the basis for the decision to treat or not to treat HCV infection. Patients with all *IFNL3* genotypes can respond to HCV therapy, and the differences in outcome are reduced with the addition of protease inhibitors. *IFNL3* genotype is one of several factors to be considered when estimating the likelihood of treatment response. In addition, the side-effect profile of HCV regimens should be considered independently from the likelihood of response according to *IFNL3* genotype.

Disclaimer

The Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines reflect expert consensus based on clinical evidence and peer-reviewed literature available at the time they are written and are intended only to assist clinicians in decision making and to identify questions for further research. New evidence may have emerged since the time a guideline was submitted for publication. Guidelines are limited in scope and are not applicable to interventions or diseases not specifically identified. Guidelines do not account for all individual variations among patients and cannot be considered inclusive of all proper methods of care or exclusive of other treatments. It remains the responsibility of the health-care provider to determine the best course of treatment for a patient. Adherence to any guideline is voluntary, with the ultimate determination regarding its application to be made solely by the clinician and the patient. CPIC assumes no responsibility for any injury to persons or damage to persons or property arising out of or related to any use of the guidelines of the CPIC or for any errors or omissions.

Implementation of the Guideline

Description of Implementation Strategy

An implementation strategy was not provided.

Implementation Tools

Resources

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Getting Better

Living with Illness

IOM Domain

Effectiveness

Identifying Information and Availability

Bibliographic Source(s)

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Adaptation

Not applicable: The guideline was not adapted from another source.

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2014 Feb

Guideline Developer(s)

Clinical Pharmacogenetics Implementation Consortium - Independent Expert Panel

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Guideline Committee

Not stated

Composition of Group That Authored the Guideline

Authors: AJ Muir, Division of Gastroenterology, Department of Medicine, Duke Clinical Research Institute, Duke University School of Medicine, Durham, North Carolina, USA; L Gong, Department of Genetics, Stanford University, Palo Alto, California, USA; SG Johnson, Department of Clinical Pharmacy, Skaggs School of Pharmacy and Pharmaceutical Sciences, University of Colorado, Denver, Colorado, USA, Clinical Pharmacy Services, Kaiser Permanente Colorado, Denver, Colorado, USA; MTM Lee, Laboratory for International Alliance on Genomic Research, RIKEN Center for Genomic Medicine, Yokohama, Japan, National Center for Genome Medicine, Institute of Biomedical Sciences, Academia Sinica, Taipei, Taiwan, School of Chinese Medicine, China Medical University, Taichung, Taiwan; MS Williams, Genomic Medicine Institute, Geisinger Health System, Danville, Pennsylvania, USA; TE Klein, Department of Genetics, Stanford University, Palo Alto, California, USA; KE Caudle, Department of Pharmaceutical Sciences, St. Jude Children's Research Hospital, Memphis, Tennessee, USA; and DR Nelson, Department of Medicine, University of Florida, Gainesville, Florida, USA

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Guideline Status

This is the current release of the guideline.

Guideline Availability

Electronic copies: Available from the Pharmacogenomics Knowledgebase Web site .

Availability of Companion Documents

The following are available:

- Supplementary material, including tables and methodological information, is available from the Pharmacogenomics Knowledgebase Web site .
- An interactive dosing table is available from the Pharmacogenomics Knowledgebase Web site .

Patient Resources

None provided

NGC Status

This NGC summary was completed by ECRI Institute on July 9, 2014. The information was verified by the guideline developer on August 13, 2014.

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